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INTELLECTUAL PROPERTY INDIA

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.

I, the undersigned, being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application*** *and* ***Complete Specification*** *filed in connection with Application for Patent No.* ***903/Del/02*** *dated* ***4th September 2002.***

Witness my hand this 29th Day of September 2003.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

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- 4 SEP 2002

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 5 (2), 7, 54 and 135 and rule 33A)

1 We, **RANBAXY LABORATORIES LIMITED,** a Company incorporated under the Companies Act, 1956 of 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"A PROCESS FOR THE PREPARATION OF TASTE MASKED DOSAGE FORMS"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. DEEPAK MURPANI

b. VINOD KUMAR ARORA

c. RAJIV MALIK

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana).
INDIA.
Tel. No. (91-124) 6343126, 6342001 – 10
Fax No. (91-124) 6342027

DUPLICATE

6. Following declaration was given by the inventors in the convention country:

We, DEEPAK MURPANI, VINOD KUMAR ARORA, RAJIV MALIK of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a. (DEEPAK MURPANI)

b. (VINOD KUMAR ARORA)

c. (RAJIV MALIK)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

a. Complete Specification (3 copies)
b. Statement and Undertaking on FORM – 3
c. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. **683513** dated **29.07.2002** on **ANZ Grindlays Bank, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this 4th day of **September,** 2002.

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
COMPANY SECRETARY

0903-02

- 4 SEP 2002

FORM 2

The Patents Act, 1970
(39 of 1970)

COMPLETE SPECIFICATION
(See Section 10)

A PROCESS FOR THE PREPARATION OF TASTE MASKED DOSAGE FORMS

DUPLICATE

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to a process for the preparation of taste masked dosage forms.

Many persons, especially the children and older persons have trouble swallowing whole tablets and even capsules. Therefore it is desirable to provide the medicine either in liquid dosage form or in a fast dissolving or disintegrating solid dosage form. Fast dissolving or disintegrating solid dosage forms, due to ease of administration and pleasant taste may encourage a patient to adhere to a daily medication regimen and therefore provide better compliance. These dosage forms combine the advantages of both liquid and conventional tablet formulations, and also offer advantage over both traditional dosage forms. It provides the convenience of a tablet formulation, while also allowing the ease of swallowing provided by a liquid formulation. It also allows the luxury of much more accurate dosing than the primary alternative, oral liquids.

Palatability and "mouth feel" are important characteristics to be considered in providing fast dissolving or disintegrating solid dosage forms, or matrix, for an active pharmaceutical medicament. Unfortunately, many active ingredients have a bitter or otherwise unpalatable taste, or an unacceptable mouth feel. In some cases, adding chemicals mediating, flavoring or sweetening ingredients to the composition can overpower the taste of the active ingredient.

However active ingredient modifying approaches are used when chemicals mediating, flavoring or sweetening agents are not effective. The dosage form is formulated so that active ingredient's dissolution in the mouth is retarded or prevented by physical and/or chemical means. One such physical approach is to embed or encapsulate the active ingredient with a wall or barrier material that physically separates it from the saliva. Cationic copolymers synthesized from dimethylaminoethyl methacrylate and neutral methacrylic acid have been employed in various taste-masking formulations. These polymers are also known to taste mask by chemically interacting with active ingredients.

For instance, U.S. Pat. No. 5,286,489 discloses a method of preparation of taste masked dosage form of active ingredient having an amine or amido groups by making a porous drug-polymer matrix with Eudragit® E-100.

Further U.S. Pat. No. 5,275,823 discloses a chewable tablet comprising granulate of a histamine H2-receptor antagonist and Eudragit E® 100, and an admixture of a taste-masking extragranular water-insoluble hygroscopic excipient.

U.S. Pat. No. 5,489,436 discloses a chewable medicament tablet comprising a medicament coated with a taste-masking amount of a polymer blend of dimethylaminoethyl methacrylate and neutral methacrylic acid esters and a polymer selected from cellulose acetate and cellulose triacetate.

U.S. Pat. No. 4,708,867 discloses a mini pellet dosage form of prednisone comprising a nonpareil seed coated with a first layer of the drug and a second layer of a copolymer of dimethylaminoethyl methacrylate and methyl methacrylate.

U.S. Pat. No. 4,760,093 discloses a taste neutral powder form of spray-dried acetaminophen which consists essentially of about 60% to 74% by weight acetaminophen and about 26% to 40% by weight of a copolymer, cationic in character, based on dimethylaminoethyl methacrylate and neutral methacrylic acid esters.

U.S. Pat. No. 6,153,220 discloses use of cationic copolymers synthesized from dimethylaminoethyl methacrylate and neutral methacrylic acid esters in amounts significantly greater than the amount of drug in need of taste masking to form with the drug a taste masked micromatrix powder. The drug and the copolymer such as Eudragit® E 100 comprise micromatrices having an average size from about 1 μm to 125 μm, preferably average particle sizes from about 5 μm to 30 μm.

Most of the processes used for taste masking in the patents listed above involve multiple steps and therefore may be technically complicated and difficult to reproduce besides being non-economical. Moreover the recommended limit by FDA for oral intake of Eudragit® E-100 and other cationic polymer with a dimethylaminoethyl ammonium group is quite low and therefore these polymers in practice cannot be used in higher amounts.

In the present invention we have discovered a novel single step process for the preparation of a taste masked dosage form which requires low amounts of cationic polymer.

The present invention therefore provides a process for preparation of a taste masked dosage form of unpleasant tasting drugs wherein the process comprises loading of a solution/dispersion of drug and a cationic polymer with a dimethylaminoethyl ammonium group on to an inert core.

The drug to polymer ratio being preferably ≤ 1:2.

In the present invention drug and polymer are dispersed/ dissolved in a solvent and this solution or dispersion is loaded on the inert core. Unlike other processes wherein a separated drug and polymer coat is given, the present invention provides a single step process. Moreover the quantity of the polymer required to mask the taste of the drug is less, which is not only economical, but also provides better maneuverability for other excipients. Further it provides a physical polymeric barrier, which completely embeds/surrounds the drug particles unlike in other coating processes where particle shape or deposition in dead zone may not allow complete particle coating. Further as the drug and polymer get mixed intimately, it prevents breaking of taste masking coating by mastication. Moreover complete solubility of cationic polymer with a dimethylaminoethyl ammonium group in acidic pH assures complete drug dissolution in upper GIT.

These drug-loaded cores may be used in oral dosage forms such as sprinkles, chewable tablets, mouth dissolving tablets, water dispersible tablets, effervescent tablets and suspensions.

For the purpose of the present invention the drugs having unpleasant taste may be selected from a H2 receptor antagonists, antibiotics, analgesics, cardiovascular agents, peptides or proteins, hormones, anti-migraine agents, anti-coagulant agents, anti-emetic agents, anti-hypertensive agents, narcotic antagonists, chelating agents, anti-anginal agents, chemotherapy agents, sedatives, anti-neoplastics, prostaglandins, drugs for erectile dysfunction, drugs acting on central nervous system, anti-diarrhoeal and antidiuretic agents.

Typical drug candidates of above therapeutic categories include but are not limited to nizatidine, cimetidine, ranitidine, famotidine, roxatidine, etinidine, lupitidine, nifentidine, niperitone,

sulfotidine, tuvatidine, zaltidine, erythomycin, penicillin, ampicillin, roxithromycin, clarithromycin, psylium, ciprofloxacin, theophylline, nifedipine, prednisone, prednisolone, ketoprofen, acetaminophen, ibuprofen, dexibuprofen lysinate, flurbiprofen, naproxen, codeine, morphine, sodium diclofenac, acetylsalicylic acid, caffeine, pseudoephedrine, phenylpropanolamine, diphenhydramine, chlorpheniramine, dextromethorphan, berberine, mefenamic acid, flufenamic acid, astemizole, terfenadine, phenytoin, guiafenesin, N-acetylprocainamide hydrochloride, and pharmaceutically acceptable salts or derivatives thereof.

However the process is more suitable for low dose drugs such as enalapril; lorazepam; zolmitriptan; domperidon; selegiline; ondansetron; mirtazepine; hyosyamine sulphate; risperidone; citalopram; olanzapine; rizatriptan; piroxicam; desloratadine, cetirizine, loperamide, sildenafil and topiramate.

For the purpose of the present invention cationic polymer with a dimethylaminoethyl ammonium groups may be selected from polymers commercially available as Eudragit® by Rohm Pharma, Germany. Preferred Eudragit® are Eudragit® E-100 and Eudragit® EPO. Eudragit® E-100 and Eudragit® EPO become water soluble via salt formation with acids, thus providing gastrosoluble film coatings. Eudragit® E films swell and are permeable in water and buffer solutions above pH 5. It is soluble in gastric fluid below pH 5. The average molecular weight of Eudragit® E is about 150,000 and it neither contains any plasticizers nor requires their addition for processing.

The Eudragit® E-100 is present in an amount sufficient to mask the otherwise disagreeable taste of the medicament while in the mouth of the user. The drug to Eudragit® ratio is $\leq$ 1:2, preferably about 1: 1.75.

Optionally substances like cellulose ester, talc, magnesium stearate and pigments may be added as these decrease the tendency of the Eudragit® polymer to agglomerate and produces a more uniform surface on the resultant nonpareil seed. Preferred cellulose ester may be selected from cellulose acetate, cellulose acetate butyrate, cellulose triacetate, ethyl cellulose or mixtures thereof.

A wide variety of organic solvents may be used to prepare the solution/ dispersion of the drug and polymer. For example solvents like acetone, methanol, ethyl alcohol, isopropyl alcohol alone or in mixture with water may be used. Other solvents which may be used are n-butyl alcohol, propylene glycol, ethylene glycol, monobutyl ether, methyl ethyl ketone, cyclohexanone, methylene chloride, chloroform, carbon tetrachloride, trichloroethylene, tetrachloroethylene, ethyl acetate, n-butyl acetate, propylene glycol acetate, toluene or mixtures thereof.

The inert core may be water soluble or insoluble particles ideally having a size >100 microns. The inert core may be selected from directly compressible dibasic calcium phosphate, directly compressible sugar, microcrystalline cellulose, directly compressible mannitol or nonpareil sugar seeds.

Non pareil seeds marketed by different manufacturers under different trade names may be used. These are available in different sizes ranging from 20 to 2000 microns.

Directly compressible mannitol commercially available as PEARLITOL® SD 200 by ROQUETTE FRERES S.A., France may be used.

Microcrystalline cellulose commercially available as Ethispheres® may be used. Ethispheres are made of 100 % microcrystalline cellulose. Ethispheres offer a good alternative for sugar-sensitive users. These are available in 200 to 1000 micron sizes.

The process of the present invention may be carried out by dissolving the drug and polymer in a suitable solvent and loading the solution on to the inert core. This loading may be carried out by granulation, spray coating or coacervation techniques.

For spray coating the polymer and drug are dissolved in the solvent and the drug-polymer solution is then sprayed onto the inert core, using a fluidized bed coater such as Glatt Fluid Bed Wurster HS Coater. Air is passed through a bed of the inert core particles to fluidize them, and the solvent solution of the drug- polymer is sprayed onto the fluidized bed. The air passing through the bed dries the loaded core particles. The drug loaded cores may then be used in combination with various excipients, flavors, and colors to make a chewable, water dispersible

or mouth dissolving tablet. These drug loaded cores may also be placed in a capsule to provide the sprinkle capsules or may be suspended in suitable solvent to make suspensions.

Loading by granulation process may be carried out by conventional techniques using the rapid mixer granulator or fluid bed granulator.

For loading by coacervation process homogenizer may be used.

The present invention is further exemplified by the following examples however these should not be construed as limiting the scope of the invention.

EXAMPLE 1

Ingredient	**Quantity (mg)**
Topiramate	15
Eudragit® EPO	26
Ethyl cellulose (low viscosity)	3.7
Titanium dioxide	1.0
Nonpareil seeds	45.3
Talc	8.9
Isopropylalcohol / Water (3:1)	q.s.
Total	100

Process:

Weighed quantity of topiramate, Eudragit® EPO and ethyl cellulose were dissolved in a suitable quantity of isopropyl alcohol / water mixture to prepare drug polymer solution. Talc and titanium dioxide were then added to the above solution. Nonpareil seeds were taken in a Glatt Fluid Bed Wurster HS Coater and drug polymer solution was sprayed on them. Coated beads

were cured by keeping them at room temperature for 24 hours. These coated beads were filled into a hard gelatin capsule.

EXAMPLE 2

Ingredient	Quantity (mg)
Desloratadine	5.05
Eudragit® E PO	7.50
Ethyl cellulose	5.0
Talc	5.0
Isopropylalcohol	q.s.
Water	q.s.
Nonpareil seeds	20.0
Total	42.55

Process:

Weighed quantity of desloratadine, Eudragit® EPO and ethyl cellulose were dissolved in a suitable quantity of isopropyl alcohol / water mixture to prepare drug polymer solution. Talc was then added to the above solution. Nonpareil seeds were taken in Glatt Fluid Bed Wurster HS Coater and drug polymer solution was sprayed on them. Coated beads were cured by keeping them at room temperature for 24 hours. These coated beads were filled into a hard gelatin capsule.

EXAMPLE 3

Ingredient	Quantity (gm)
Desloratadine	20.2
Eudragit® E PO	30.0
Ethyl cellulose	20.0
Talc	20.0
Isopropylalcohol	150 ml
Water	50 ml
Nonpareil seeds	80.0
Total	170.20

Process: same as for Example-2.

WE CLAIM:

1. A process for preparation of a taste masked dosage form of unpleasant tasting drugs wherein the process comprises loading of a solution/dispersion of a drug and a cationic polymer with a dimethylaminoethyl ammonium group on to an inert core.

2. The process according to claim 1 wherein drug to polymer ratio is ≤ 1:2.

3. The process according to claim 2 wherein drug to polymer ratio is 1:1.75.

4. The process according to claim 1 wherein unpleasant tasting drug may be selected from the group consisting of H2 receptor antagonists, antibiotics, analgesics, cardiovascular agents, peptides or proteins, hormones, anti-migraine agents, anti-coagulant agents, anti-emetic agents, anti-hypertensive agents, narcotic antagonists, chelating agents, anti-anginal agents, chemotherapeutic agents, sedatives, anti-neoplastics, prostaglandins, drugs for erectile dysfunction, drugs acting on central nervous system, anti-diarrhoeal and anti-diuretic agents.

5. The process according to claim 4 wherein the typical unpleasant tasting drugs candidates are nizatidine, cimetidine, ranitidine, famotidine, roxatidine, etinidine, lupitidine, nifentidine, niperitone, sulfotidine, tuvatidine, zaltidine, erythomycin, penicillin, ampicillin, roxithromycin, clarithromycin, psylium, ciprofloxacin, theophylline, nifedipine, prednisone, prednisolone, ketoprofen, acetaminophen, ibuprofen, dexibuprofen lysinate, flurbiprofen, naproxen, codeine, morphine, sodium diclofenac, acetylsalicylic acid, caffeine, pseudoephedrine, phenylpropanolamine, diphenhydramine, chlorpheniramine, dextromethorphan, berberine, mefenamic acid, flufenamic acid, astemizole, terfenadine, phenytoin, guiafenesin, N-acetylprocainamide HCl and pharmaceutically acceptable salts or derivatives thereof.

6. The process according to claim 1 wherein unpleasant tasting drug has a low dose.

7. The process according to claim 6 wherein the low dose drug may be selected from enalapril; lorazepam; zolmitriptan; domperidon; selegiline; ondansetron; mirtazepine; hyosyamine sulphate; risperidone; citalopram; olanzapine; rizatriptan; piroxicam; desloratadine, cetirizine, loperamide, sildenafil and topiramate.

8. The process according to claim 7 wherein the drug is topiramate.

9. The process according to claim 7 wherein the drug is desloratadine.

10. The process according to claim 7 wherein the drug is sildenafil.

11. The process according to claim 7 wherein the drug is olanzapine.

12. The process according to claim 7 wherein the drug is citalopram.

13. The process according to claim 7 wherein the drug is ondansetron.

14. The process according to claim 7 wherein the drug is loperamide.

15. The process according to claim 7 wherein the drug is cetirizine.

16. The process according to claim 1 wherein the cationic polymer with a dimethylaminoethyl ammonium groups may be selected from polymers commercially available as Eudragit®.

17. The process according to claim 16 wherein the Eudragits® is Eudragit® E-100 or Eudragit® EPO.

18. The process according to claim 17 wherein the Eudragit® is Eudragit® E-100.

19. The process according to claim 17 wherein the Eudragit® is Eudragit® EPO.

20. The process according to claim 1 wherein the drug polymer solution/dispersion further contains additives.

21. The process according to claim 20 wherein additives are selected from cellulose ester, talc, magnesium stearate and pigments.

22. The process according to claim 21 wherein cellulose ester is cellulose acetate, cellulose acetate butyrate, cellulose triacetate, ethyl cellulose or mixtures thereof.

23. The process according to claim 1 wherein drug polymer solution/dispersion is prepared in a solvent.

24. The process according to claim 23 wherein solvent is selected from acetone, methanol, ethyl alcohol, ethyl alcohol, isopropyl alcohol alone or in mixture with water, n-butyl alcohol, propylene glycol, ethylene glycol, monobutyl ether, methyl ethyl ketone, cyclohexanone, methylene chloride, chloroform, carbon tetrachloride, trichloroethylene, tetrachloroethylene, ethyl acetate, n-butyl acetate, propylene glycol acetate, toluene or mixtures thereof.

25. The process according to claim 1 wherein inert core is water soluble or insoluble.

26. The process according to claim 25 wherein water soluble or insoluble inert core may be selected from directly compressible dibasic calcium phosphate, directly compressible sugar, microcrystalline cellulose, directly compressible mannitol or nonpareil sugar seeds.

27. The process according to claim 26 wherein inert core is directly compressible dibasic calcium phosphate.

28. The process according to claim 26 wherein inert core is directly compressible sugar.

29. The process according to claim 26 wherein inert core is microcrystalline cellulose.

30. The process according to claim 29 wherein microcrystalline cellulose is Ethisphere®.

31. The process according to claim 26 wherein inert core is directly compressible mannitol.

32. The process according to claim 31 wherein directly compressible mannitol is Pearlitol®.

33. The process according to claim 26 wherein inert core is nonpareil sugar seed.

34. The process according to claim 1 wherein the inert core has a particle size greater than about 100 microns.

35. The process according to claim 1 wherein loading of drug polymer solution/dispersion is carried out by granulation, spray coating or coacervation techniques.

36. The process according to claim 35 wherein loading of drug polymer solution/dispersion is carried out by spray coating.

37. The process according to claim 35 wherein loading of drug polymer solution/dispersion is carried out by granulation.

38. The process according to claim 35 wherein loading of drug polymer solution/dispersion is carried out by coacervation techniques.

39. The process according to claim 1 wherein the dosage form is sprinkles, chewable tablets, mouth dissolving tablets, water dispersible tablets, effervescent tablets and suspensions.

40. The process according to claim 39 wherein the dosage form is sprinkles.

41. The process according to claim 39 wherein the dosage form is chewable tablet.

42. The process according to claim 39 wherein the dosage form is mouth dissolving tablet.

43. The process according to claim 39 wherein the dosage form is water dispersible tablet.

44. The process according to claim 39 wherein the dosage form is effervescent tablet.

45. The process according to claim 39 wherein the dosage form is suspension.

46. A process for preparation of a taste masked dosage form of unpleasant tasting drug as described and exemplified herein.

Dated this 4TH day of **September, 2002.**

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary